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L3: Entry 1 of 1 File: PGPB Jun 17, 2004

DOCUMENT-IDENTIFIER: US 20040115770 A1
TITLE: Polypeptides for increasing mutant CFTR channel activity

Pre-Grant Publication (PGPub) Document Number:
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Detail Description Paragraph:
[0042] In yet another embodiment of the invention, the CFTR polypeptides of the invention, including those with or without an internalizing peptide sequence, may further comprise a secretion leader sequence that directs secretion of polypeptides across the cell membrane. Following recombinant expression and secretion of such CFTR polypeptides, the secreted CFTR polypeptides may transduce neighboring cells and/or enter the bloodstream where cells at a distance can be transduced thereby restoring CFTR channel activity to the transduced cells.

Detail Description Paragraph:
[0043] The CFTR polypeptides of the invention, including those linked to a internalizing peptide and/or a secretion leader sequence, can be synthesized using a variety of different methods. Such methods include solid-phase peptide synthesis (spps) as described in Coligan et al. (Current Protocols in Protein Science, 1995-2002, John Wiley & Sons, Inc.). In addition, cloning techniques known in the art may be used for cloning of a nucleic acid molecule encoding the CFTR polypeptide of interest into an expression vector. Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al. (eds.), 1993, Current Protocols in Molecular Biology, John Wiley & Sons, NY; and Kriegler, 1990, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY.

Detail Description Paragraph:
[0060] In another embodiment of the invention, a nucleic acid molecule capable of encoding a CFTR polypeptide comprising a secretion leader sequence may be transferred into a host cell for recombinant expression of the secreted CFTR polypeptide. Upon secretion, the CFTR polypeptide will transduce neighboring cells and/or enter the bloodstream where cells can be transduced at a distance. Secretion sequences that may be utilized are know to those of skill in the art. Such sequences include but are not limited to those of the herpes simplex VP22 protein (Elliot, 1999 Gene Therapy 6:149-51).

CLAIMS:

6. The method of claim one wherein the CFTR polypeptide further comprises a secretion leader sequence.

14. The method of claim 9 wherein the CFTR polypeptide further comprises a secretion leader sequence.

20. The peptide of claim 17 or 19 further comprising a secretion leader sequence.

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REPRESENTATIVE-FIGURES: NONE

ABSTRACT:

The present invention provides methods and compositions for enhancing channel activity to the mutant cystic fibrosis trans-membrane conductance regulator protein (CFTR). The compositions of the invention comprise polypeptides containing CFTR sub-domains that are designed to mimic the folding defect of the full length mutant CFTR proteins, resulting in competitive binding to cytoplasmic chaperones such as Hsc/Hsp70 and Hdj2. The methods of the invention comprise transduction, or recombinant expression, of CFTR polypeptides in a cell expressing mutant CFTR. The presence of the CFTR polypeptide results in a dominant effect whereby the CFTR polypeptide competes with the endogenously expressed mutant CFTR for binding to cytoplasmic chaperones such as Hsc/Hsp70 and Hdj2. Mutant CFTR proteins include, but are not limited to, .DELTA.F508 CFTR. The present invention is based on the discovery that reduced binding of cytoplasmic chaperones

to the endogenous .DELTA.F508 CFTR, mediated by the presence of CFTR polypeptides, results in restoration of plasma membrane localization and channel activity. The methods and compositions of the invention can be used to restore channel activity in cystic fibrosis subjects carrying genetic defects in the CFTR gene, such as for example, .DELTA.F508 CFTR.

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